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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,009	GEALL, ANDREW	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/06 & 6/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-28 are under consideration in this office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on January 13, 2006 and June 8, 2005 have been entered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-2, 5, 8-10, 15-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans (WO 02/00844 published January 3, 2002).

The claims are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; and (iv) an amorphous cryoprotectant or a crystalline bulking agent; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture. The dependant claims are drawn to the general formula and specific types of the block copolymer, the cationic surfactant, buffer agents, and amount of the components.

Evans teach polynucleotide vaccine adjuvants and formulations containing surfactants. Evans teach the preparation of compositions which comprise polynucleotide vaccine adjuvants having a block copolymer and a cationic surfactant (page 3, lines 5-8). Evans also teach the use of nonionic block copolymers such as polyoxyethylene (POE)/polyoxypropylene (POP) are taught (page 3, lines 31-34).

Evans recites a general POE/POP formula: $HO(C_2H_4O)_a(C_3H_60)_b(C_2H_40)_a H$, wherein (b) represents a number such that the molecular weight of the hydrophobic POP portion (C_3H_60) is less than 20,000 daltons and wherein (a) represents a number such that the percentage of hydrophilic POE portion (C_2H_4O) is between approximately 1% and 40% by weight (page 4, lines 10-17). Therefore Evans teach the claimed block copolymers having the general formula and ranges as recited by Claim 2. Evans discloses surface-active copolymer having a structure represented by CRL-005 (page 13, lines 19-21), just as recited by claim 8. The adjuvanted polynucleotide vaccine formulations of the present invention also comprise a cationic surfactant along with the block copolymer (page 13, lines 22-26). Cationic surfactants which may be used include but are not limited to: benzalkonium chloride (BAK), benzethonium chloride, cetramide (which contains tetradecyltrimethylammonium bromide, dedecyltrimethylammonium bromide hexadecyltrimethyl ammonium bromide, cetylpyridinium chloride and cetyl trimethylammonium chloride (page 13, lines 26-34). Thus, Evans teach the same cationic surfactants recited by claim 9. It is preferred that the concentration range of a respective polynucleotide be from about 0.5 mg/ml to about 7.5 mg/ml, the POE and POP block copolymer be at a concentration of from about 1 to about 70 mg/m1 and that

the cationic surfactant(s) be at a concentration of 0.1 to 10mM (pages 21-22, lines 32-1). Thus the ranges for the cationic surfactant, the block copolymer and the polynucleotide from claims 20-22 are disclosed.

Evans teach the Preparation of CRL-1005 formulations containing DNA and the cationic surfactant by mixing or vortexing the components at temperatures below the cloud point of the polymer, approximately 6-7°C (page 32, lines 23-34). Therefore, Evans teach mixing the instantly recited components at temperatures below the cloud point and within the recited range of claim 5. It is also useful to provide formulations that provide for long-term stability of the vaccines (page 30, lines 22-23). Evans states that stabilized vaccines and alternative formulations have been taught by the incorporated WO 97/40839 reference (page 31, lines 15-18). WO 97/40839 teach the lyophilization of DNA vaccines in the presence of appropriate formulation excipients (page 9, lines 23-25). The physiologically acceptable buffer is Tris-HCl, while Figure 3 shows the use of 10mM phosphate buffer (page 13, lines 5-27). Thus the art teaches the use of sodium phosphate buffer within the instantly recited ranges.

The composition can also comprise other excipients, including but not limited to excipients known in the art such as glycerol (page 23, lines 10-14). Therefore, Evans teach the inclusion of glycerol, an amorphous cryoprotectant, as defined by the specification at paragraph [0079]. The vaccines may be formulated in any pharmaceutically effective formulation and may include a saline solution such as phosphate buffered saline (PBS) (page 30, lines 18-20). Furthermore, Evans teach specific buffer types, pH, salt concentration, light exposure, as well as specific types of

sterilization process used to prepare the products (page 30, lines 33-34). The buffer may be phosphate or bicarbonate with a pH in the range of 7-8 (page 31, lines 4-6). The Preparation of CRL-1005 formulations includes the use of PBS (page 32, lines 23-34). Thus a pH stabilizing physiologic buffer is taught, just as required by claims 15-16.

Therefore Evans teach a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer such as CRL-1005; (ii) a polynucleotide; (iii) an instantly recited cationic surfactant; (iv) an glycerol amorphous cryoprotectant; and a physiological buffer at a temperature below the cloud point of said block copolymer to form a mixture and having the recited concentrations and (b) lyophilizing the mixture, just as instantly claimed.

4. Claims 23-24 and 27-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans (WO 02/00844 published January 3, 2002).

The claims are drawn to a stable, monodispersed product produced by the method of claims 1 and 15.

The teachings of Evans have been set forth above. Evans clearly teaches a composition comprising a POE and POP block copolymer; a polynucleotide; a cationic surfactant; and a glycerol amorphous cryoprotectant or a crystalline bulking agent.

Therefore, Evans clearly teaches the instantly claimed product by process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844 published January 3, 2002) in view of Balasubramaniam (US Patent 5,824,322).

The claims are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; and the other recited components wherein the block copolymer has the general formula recited by Claim 3.

The teachings of Evans has been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. In additions the art teaches the use of POE-POP-POE copolymers such as CRL-1005 and Evans even taught the use of PLURONIC™ copolymers, which have the general organization POP-POE-POP required, see page 22, line 20. However Evans did not teach a POP-POE-POP copolymer wherein POP accounted for up to 20,000 daltons of the mass of the copolymer and POE represented between 1% and 50% of the copolymer by weight.

Balasubramaniam teach compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene having the formula: $HO(C_3H_60)_b(C_2H_4O)_a(C_3H_60)_bH$, wherein (b) represents a number such

that the molecular weight of the hydrophobe $(C_3H_60)_b$ that is between approximately 2,000 and 10,000 daltons and (a) represents a number such that the percentage of hydrophile (C_2H_4O) is between approximately 2% and 30% by weight (col. 13, lines 25-37). These compositions have many beneficial properties including but not limited to stimulating T-cell immune system, the growth of the thymus, the production of bone marrow cells, accelerating and prolonging growth, and having ionophore activity (col. 14, lines 24-68). The preparations may also contain may include a saline solution such as physiologic phosphate buffered saline (PBS) or other physiologic salt solutions (col. 21, lines 17-20). Furthermore, Balasubramaniam teach that such formulations may be presented and stored in freeze-dried (lyophilized) conditions only requiring the addition of sterile water prior to use (col. 24, lines 60-64).

Therefore it would have been *prima facie* obvious at the time of applicants' invention to modify the method of preparation as taught by Evans to include the reverse triblock copolymer of polyoxyethylene/polyoxypropylene, as taught by Balasubramaniam. One of ordinary skill in the art would have been motivated to do so because Evans already teach the use of similar POP-POE-POP copolymers in lyophilized composition and Balasubramaniam teach several beneficial properties associated with the compositions comprising the copolymers. Furthermore, no more than routine skill would have been required to exchange and use a functionally equivalent block copolymer in the method for preparing a lyophilized composition when the prior art teaches its advantageous properties.

6. Claims 4 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844 published January 3, 2002) in view of Hunter et al., (US Patent 5,811,088).

The claims are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; and the other recited components wherein the method further comprises a cold filtration step at a temperature of about –2 to 8°C using a filter. The teachings of Evans has been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. However Evans did not teach a cold filtration step.

Hunter et al., teach compositions comprising a surface active copolymer having the general formula $HO(C_2H_4O)_b(C_3H_60)_a(C_2H_40)_bH$, wherein (a) represents an integer such that the hydrophobe represented y (C_3H_60) has a molecular weight of about 1,200 to about 15,000 daltons and wherein (b) represents an integer such that the hydrophile portion represented by (C_2H_4O) constitutes approximately 1% and 50% by weight of the compound (col. 5, lines 1-17). The composition may also comprise surfactants and low molecular weights (col. 8, lines 60-63). Hunter et al., teach preparation and solubilization of copolymers in an ice-cold phosphate buffered saline (col. 18, lines 41-43). The cold solution was filter sterilized on 0.22um filters and stored at 4°C (col. 18, lines 43-45).

Therefore it would have been *prima facie* obvious at the time of applicants' invention to cold filter formulations containing block copolymers at a temperature at

which they are soluble, i.e., below their cloud point, just as Evans teaches. Thus, one of ordinary skill in the art would have a reasonable expectation of success in saving time and materials to sterilize the compositions after they had been mixed and rather than separately and individually treat the components. Therefore, no more than routine skill would have been required to cold filter the mixture, since the prior art teaches that such techniques are well known to create sterile compositions.

7. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844 published January 3, 2002) in view of Hunter et al., (US Patent 5,811,088).

The claims are drawn to a stable, monodispersed product produced by the method of claim 4.

The teachings of Evans and Hunter et al., have been set forth above. Evans and Hunter clearly teach a composition comprising a POE and POP block copolymer; a polynucleotide; a cationic surfactant; and an amorphous cryoprotectant or a crystalline bulking agent.

Therefore it would have been *prima facie* obvious at the time of applicants' invention to cold filter formulations containing block copolymers at a temperature at which they are soluble, i.e., below their cloud point, just as Evans teaches. Thus, one of ordinary skill in the art would have a reasonable expectation of success in saving time and materials to sterilize the compositions after they had been mixed and rather than separately and individually treat the components. Therefore, no more than routine skill

would have been required to produce a stable, monodispersed product produced by the cold filter method, since the prior art teaches that such techniques are well known to create sterile compositions. Therefore, Evans and Hunter et al., clearly teach the instantly claimed product by process.

8. Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844 published January 3, 2002) in view of Munsunuri et al., (WO 99/21591).

The claims are drawn to a method of preparing a lyophilized composition comprising mixing the recited components wherein the method further comprises sucrose as the cryprotectant and/or the crystalline bulking gent at the instantly recited ranges. The teachings of Evans have been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. However Evans did not teach mixing sucrose as the cryprotectant at the instantly recited ranges.

Munsunuri et al., teach composition soluble ionic complexes comprising a surfactant and a polynucleic acid sequence (page 4, lines 1-5). The composition may contain other agents such as aqueous buffers, like phosphate buffered saline for use in forming the complexes in concentrations of about 2 to about 50 mM (page 12, lines 19-29). Thus the art teaches the use of physiologic buffers in the mixture within the instantly recited ranges. The compositions may also include sucrose, mannitol, sorbitol and trehalose (page 13, lines 4-8). For example sucrose is present in the admixture in a

concentration of about 0 to about 9.25% w/v, or concentrations greater than 9%w/v wherein one skilled in the art of pharmaceutical preparations can readily adjust this characteristic of the complex (page 13, lines 8-12). Example 1 shows the mixing of a compositions comprising the surfactant, the polynucleic acid sequences, a phosphate buffer, tonicity agents such as sucrose, mannitol, trehalose or any other non-ionic agent (page 30, lines 13-21). It is noted that the instant specification, at pages 22-23, names sucrose and sorbitol as amorphous cryoprotectants and mannitol and trehalose and crystalline bulking agents, thus the art teaches the instantly recited agents used within the instantly claimed ranges. Example 1 also shows filtering the admixtures using a commercially obtained 0.22um filter.

Therefore it would have been *prima facie* obvious at the time of applicants invention to modify the method of preparation as taught by Evans to include the sucrose cryprotectant and/or the crystalline bulking agent at the instantly recited ranges, as taught by Musunuri et al. One of ordinary skill in the art would have been motivated to incorporate additional agents within the pharmaceutical composition because Evans already teach a method of lyophilizing polynucleotides and surfactants in a composition wherein the composition may include other pharmaceutically acceptable agents. Furthermore, no more than routine skill would have been required to use additional well-known pharmaceutically acceptable agents in the method for preparing a lyophilized composition when the prior art teaches its advantageous properties.

Prior Art

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chen et al., (US Patent 6,251,599) teach stabilized nucleic acid compositions which teach lyphophilized compositions further comprising excipients, amorphous cryoprotectants and crystalline bulking agents and ligands. Emanuele et al., (US Patent 5,990,241) teach POE/POP copolymers with improved biological activity. Patel et al., (US Patent 6,248,363) teach solid carriers for improved delivery of active ingredients in pharmaceutical compositions comprising hydrophilic and phobic surfactants, and sugars such as lactose, sucrose, dextrose and polyols such as mannitol and sorbitol.

Conclusion

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, A. Mark Navarro can be reached on 571-272-0861. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
September 28, 2006